Please substitute the following amended paragraph number 20 found on Page 13 for the original paragraph having the same number:

20. The amino acid Lys has one amino group, but there is one amino group present due to the peptide backbone structure. Therefore, this peptide can react with two equivalents of an amino group specific reagent, such as the N-hydroxysuccinimide activated ester of biotin to give:

(biotin)Lys(biotin)- Cys(PEG)-Cys(PEG)-Cys(PEG) (SEQ ID NO: 12)

where by convention, the biotin that reacts due to the peptide backbone structure is written at the extreme left and the biotin associated with the Lys is written in parentheses.

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Thus, a peptide acting as a scaffold of the formula: $(Lys)_n$-$(Cys)_m$ can be derivatized using two orthogonal reactions to give a product with exactly n+1 copies of the amine-reactive chemical and m copies of the thiol-reactive chemical. By being orthogonal, these 2 reactions can be carried out with either the thiol or the amino reaction first and without regard to any significant improper cross-reaction occuring.

Please substitute the following amended paragraph number 29 found on Pages 16-17 for the original paragraph having the same number:

29. The therapeutic or diagnostic agent comprising a thiol group may be a synthetic or naturally-occurring protein or peptide. It may also be a therapeutic agent or a diagnostic agent with or modified to have a thiol group, or be conjugatable to a thiol group, such a modified antisense oligonucleotide or a thioamide-moiety-containing therapeutic agent. It may be a small-molecule compound with a pharmacological activity. It may be a retro-inverso form of a biologically-active peptide, retro-inverso form possessing the same or similar biological activity but possessing other desirable characteristics such as decreased susceptibility to enzymatic attack or metabolic enzymes. In one non-limiting example, the peptide comprises a Tat-inhibitory polypeptide, comprising an amino acid sequence of formula I:

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R-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-X-(biotin)-Cys-NH_2 (SEQ ID NO:1), and biologically and pharmaceutically acceptable salts thereof, stereo, optical and geometrical isomers thereof where such isomers exist, as well as the pharmaceutically acceptable salts and solvates thereof, wherein R comprises the residue of a carboxylic acid or an acetyl group; and X is a Cys or Lys residue. Examples of the foregoing include

N-acetyl-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Cys-(biotin)-Cys-NH_2 (SEQ ID NO:2)

N-acetyl-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Lys-(biotin)-Cys-NH_2 (SEQ ID NO:3)

N-acetyl-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-D-Cys-(biotin)-Cys-NH_2 (SEQ ID NO:4)

N-acetyl-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-D-Lys-(biotin)-Cys-NH_2 (SEQ ID NO:5)

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N-acetyl-Gln-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-D-Lys-(biotin)-Cys-NH_2 (SEQ ID NO:6);

N-acetyl-Arg-Lys-Lys-Arg-Arg-Pro-Arg-Arg-Arg-Cys-(biotin)-Cys-NH_2 (SEQ ID NO:7); or

N-acetyl-DCys-DLys-(biotin)-DArg-DArg-DArg-DGln-DArg-DArg-DLys-DLys-DArg-NH_2 (SEQ ID NO: 8)

or biologically and pharmaceutically acceptable salts thereof.

Please substitute the following amended paragraph number 77 found on Pages 38-39 for the original paragraph having the same number:

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77. Although the foregoing results show that appending biotin as a targeting moiety may be applied as a novel and useful strategy to enhance the intestinal absorption of large peptides, due to the high affinity, low capacity nature of SMVT (Km values of substrates are typically in the low micromolar range), the resultant saturation of the transporter may limit the dose of drug that can be delivered via this transporter. In order to overcome this drawback, we evaluated the ability of a poly(ethylene glycol) (PEG)-based biopolymeric delivery vehicle to maximize the therapeutic or diagnostic payload of the peptide. As

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described above, the PEGylated delivery vehicle (or conjugate) was designed to (i) carry multiple copies of a drug, (ii) have an extended half-life in blood or extracellular fluid, (iii) enhance cellular uptake of the drug and subsequently (iv) release the appended drug molecules inside the cell. In a preliminary study, the conjugate, containing multiple copies of an 11-amino acid Tat-peptide with an appended biotin molecule, N-acetyl-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Lys(biotin)-Cys-NH_2 (SEQ ID NO: 3), displayed 5-fold greater potency (compared to the single copy Tat-peptide) in preventing Tat-dependent gene expression in a cultured cell system (which was not tested for expression of SMVT).

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Please substitute the following amended paragraph number 86 found on Pages 44-45 for the original paragraph having the same number:

86. The following abbreviations are used herein throughout. BOC: Tertiary-butyloxycarbonyl; BOP/HOBt: (benzotriazolyl-oxy-tris-(dimethylamino)-phosphonium/hexafluoro phosphate /hydroxybenzotriazole); DMF: Dimethylformamide; DIEA: N,N-diisopropylethylamine; DTT: Dithiothreitol; Fmoc: Fluorenylmethoxylcarbonyl; RI: retro-inverso; K: lysine; RI-K-Tat9: N-acetyl-D-Lys-D-Arg-D-Arg-D-Arg-D-Gln-D-Arg-D-Arg-D-Lys-D-Lys-D-Arg-NH_2 (SEQ ID NO: 9); RI-K(biotin)-Tat9: RI-K-Tat9 with biotin linked to ε-N of N-terminal D-Lys; RI-K(biotin)-Tat9-Cys: N-acetyl-D-Cys-D-Lys(ε-biotin)-D-Arg-D-Arg-D-Arg-D-Gln-D-Arg-D-Arg-D-Lys-D-Lys-D-Arg-NH_2 (SEQ ID NO: 8); SMVT: Sodium dependent multivitamin transporter; and SPDP: N-succinimidyl-3-(2-pyridylthio) propionate.

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Please substitute the following amended paragraph number 106 found on Page 57 for the original paragraph having the same number:

106. Peptide Synthesis RI-K(biotin)-Tat9, N-acetyl-D-Lys:(ε-biotin)-D-Arg-D-Arg-D-Arg-D-Gln-D-Arg-D-Arg-D-Lys-D-Lys-D-Arg-NH_2 (SEQ ID NO: 9), was synthesized manually on a PAL resin by Fmoc chemistry using reagents from PerSeptive Biosystems (Framingham, MA). Biotin was appended to the ε-amine group of the lysine

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side chain using the reagent, NHS-biotin (N-hydroxy succinimide, Pierce, Rockford, IL), as follows. After assembly of the peptide and while still attached to the solid support, the Mtt (3-(4,5-dimethyl-2-thiazyl)-2,5-diphenyl-2H-tetrazolium bromide) protecting group was removed from the lysine side chain of RI-K-Tat9 by drop-wise addition of 1% trifluoroacetic acid (TFA) in dichloromethane at the rate of 1 ml/min for 2 hours. The solid support was washed with dimethylformamide, and NHS-biotin in DMF was added at 5-fold molar excess. Conjugation with biotinylation reagent proceeded overnight with vigorous shaking. Peptides were cleaved from the support and deprotected by treatment with a mixture of 90 % TFA, 5% thioanisole, 2% anisole and 3 % ethanedithiol for 4 hours. The peptides were then purified by reverse-phase high-performance liquid chromatography and characterized by mass spectrometry for the molecular ion. Peptide concentration was determined by amino acid analysis. The synthesis of RI-K-Tat9 [N-acetyl-D-Lys-D-Arg-D-Arg-D-Arg-D-Gln-D-Arg-D-Arg-D-Lys-D-Lys-D-Arg-NH_2 (SEQ ID NO: 9)] entailed the same procedure as RI-K(biotin)-Tat9 except for attachment of biotin.

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Please substitute the following amended paragraph number 111 found on Page 61 for the original paragraph having the same number:

111. Gene Expression using Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

The presence of SMVT in Caco-2 cells and transfected CHO cells was determined using RT-PCR. Total RNA from Caco-2, CHO/hSMVT and CHO/pSPORT cells was isolated with TRIzol reagent (Promega, Madison, WI). The first strand of cDNA was synthesized using 3 μg of RNA, 2 pmol of reverse primer, 10 mM dithiothreitol, 0.5 mM dATP, dCTP, dGTP and dTTP, and 200 units of Superscript II reverse transcriptase as described by the manufacturer (GIBCO BRL). Two specific primers were synthesized based on human SMVT. The sequences for forward and reverse hSMVT primers were 5′-CTG TCC GTG CTG GCC CTG GGC-3′ (SEQ ID NO: 10) and 5′-GAC CAG GCC AAT GAG GCA GCC-3′ (SEQ ID NO: 11), respectively. PCR was performed using 50 µl of reaction volume containing 10 ng of cDNA, 0.2 mM $MgCl_2$, 0.5 μM primers, and 2.5

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